Criteria for discharge of patients with Ebola virus diseases in high-income countries

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Abstract: During the recent epidemic of Ebola virus disease (EVD) in west Africa,1 several health-care and aid workers infected with EVD were evacuated to Europe and the USA, where local transmission occurred in occupationally exposed health-care workers. Preparation for discharge requires an organised and evidence-based approach to ensure that the patient, health-care workers, family, and community are protected at all times. The risk of infection to others after discharge in the community and of unexpected late clinical events for the patient make discharge policies difficult to formulate.

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During the recent epidemic of Ebola virus disease (EVD) in west Africa,[1] several health-care and aid workers infected with EVD were evacuated to Europe and the USA, where local transmission occurred in occupationally exposed health-care workers. Preparation for discharge requires an organised and evidence-based approach to ensure that the patient, health-care workers, family, and community are protected at all times. The risk of infection to others after discharge in the community and of unexpected late clinical events for the patient make discharge policies difficult to formulate.[2]

To suggest a framework for developing international consensus on criteria for safe discharge of EVD patients from hospital in high-income countries, we searched the websites of WHO, the US Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), and Public Health England (PHE) for hospital discharge criteria using the search terms "EVD discharge", "EVD management", "Ebola discharge", and "Ebola management". We also searched PubMed, ProMed, and Embase for all published clinical reports on EVD patients cared for out of Africa during the current EVD outbreak using the search terms ("Ebola" OR "EVD") AND ("case" OR "cases" OR "case-report" OR "report" OR "patient" OR "patients") in the title or abstract. The search dates were January, 2014, to July, 2015. We also added unpublished data about EVD patients treated at the National Institute for Infectious Diseases (INMI) Lazzaro Spallanzani in Rome, Italy.

WHO guidelines recommended that, in west Africa, the discharge of an EVD case be based on improvement of the clinical conditions together with, if laboratory testing is available, a negative blood RT-PCR for Ebola virus RNA.[3] The US CDC listed eight criteria to consider when deciding whether to discharge people under investigation for Ebola virus disease, but no guideline was provided for confirmed cases.[4] The criteria included resolution of all symptoms and having no clinical laboratory results consistent with EVD. The ECDC has currently removed from the public access domain of its website a previously published expert opinion document on EVD discharge criteria for EU countries. This document recommended that EVD cases should remain in isolation until recovery from clinical symptoms of EVD and two consecutive antigen capture or RT-PCR tests on blood specimens are negative.[5] We did not find any PHE document providing formal criteria for discharge of patients with confirmed EVD. Thus, none of these widely referenced health agencies provide recommendations for discharging EVD patients cared for outside Africa.

Of 22 patients with EVD discharged from hospitals in Europe and the USA, discharge criteria were available for 14 cases (table). Different virological criteria for discharge were applied between and within the same country, ranging from two consecutive blood specimens testing negative for Ebola virus RNA by RT-PCR assay to the

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	Centre	Day of Discharge*	Discharge criteria	Comments
1	Atlanta	30	2 negative RT-PCR for EBOV on blood 24 h apart	Patient had positive urine RT-PCR for EBOV on day 28. Unspecified results on other biological fluids.
2	Atlanta	29	2 negative RT-PCR for EBOV on blood 24 h apart	Patient had repeated negativity of RT-PCR for EBOV in urine. Unspecified results on other biological fluids.
3	Atlanta	44	Negative blood and urine RT-PCR for EBOV on serial specimens	At discharge semen positive for EBOV on RT-PCR and culture
4	Dallas† Bethesda‡	15	Repeated negative RT-PCR for EBOV on blood	Throat, rectal, vaginal, urine, and sweat samples negative for EBOV on RT-PCR
5	Dallas† Atlanta‡	14	Repeated negative blood and urine RT-PCR for EBOV	Skin and vaginal swabs negative for EBOV on RT-PCR
6	Omaha	28	3 serial blood samples free of EBOV	Unspecified result of tests in other biological specimens
7	Omaha	20	3 serial blood samples free of EBOV	Unspecified result of tests in other biological specimens
8	New York	22	2 negative RT-PCR for EBOV on blood	Unspecified result of tests in other biological specimens
9	Hamburg	40	All cultures of RT-PCR positive samples of body fluids free of infectious virus for 20 days	At discharge patient had negative RT-PCR in plasma and urine; positive RT-PCR on sweat
10	Frankfurt	NA	Repeated negative blood RT-PCR for EBOV	Urine and stool samples also negative RT-PCR for EBOV
11	Madrid	34	Repeated negative RT-PCR for EBOV of all body fluid samples	Unspecified body site and number of samples
12	Rome	44	Repeated negative RT-PCR for EBOV of all body fluid samples apart from semen	Patient's throat, sweat, ocular, and stool samples negative for EBOV on RT-PCR
13	Rome	31	Repeated negative RT-PCR for EBOV of all body fluid samples apart from semen	Patient's blood, urine, throat, sweat, ocular, sputum, and stool samples negative for EBOV on RT-PCR
14	Geneva	19	Repeated negative RT-PCR for EBOV of all body fluid samples	Patient's blood, urine, sweat, ocular, saliva, and stool samples negative for EBOV on RT-PCR

EBOV=Ebola virus RNA. Atlanta=Emory University Hospital, Atlanta, GA, USA. Dallas=Texas Health Presbyterian Hospital, Dallas, TX, USA. Bethesda=National Institutes of Health Clinical Center, Bethesda, MD, USA. Omaha=Nebraska Medical Center, Omaha, NE, USA. New York=Bellevue Hospital Center, New York, NY, USA. Hamburg=University Medical Center, Hamburg, Germany. Frankfurt=University Hospital, Frankfurt, Germany. Madrid=La Paz Carlos III University Hospital, Madrid, Spain. Rome=INMI Lazzaro Spallanzani, Rome, Italy. Geneva=Geneva University Hospitals, Geneva, Switzerland. *From onset of illness. †Admitted to. ‡Transferred to.

Table: **Discharge criteria for 14 patients with Ebola virus disease managed at hospitals in Europe and the USA**

absence of Ebola virus in cell culture of several biological samples. In all but one patient, negative RT-PCR assays on biological samples were considered as common minimum requirements for discharging patients in the community. Patient 9, according to the German guidelines, was released from the hospital only when no infectious virus was isolated in cell culture. At the INMI Lazzaro Spallanzani in Rome, Italy, patients 12 and 13 were considered to be convalescent at day 28 and 17 from illness onset, respectively, since clinical symptoms resolved completely and RT-PCR on the blood became negative.[6] Despite this, the institute only discharged patients 12 and 13 after achieving negative RT-PCR assay on urine and other body fluids.

The key issues for further discussion are: (1) the clinical and virological criteria for discontinuing strict isolation and stepping down to routine hospital practice; (2) the clinical and virological criteria for discharge from hospital; (3) the virological criteria for resumption of household, community, and professional activities; (4) the follow-up of clinical and virological parameters during the convalescent phase; and (5) the definition of "cured". The value of a positive biomolecular assay in the absence of data on the infectivity of the same biological sample remains unclear and discharge criteria need to be considered in the context of viral persistence after clinical recovery. Before discharging patients home, preliminary steps to scale down isolation precautions to routine in-hospital practices were applied differently in the reported cases; in most cases, negative Ebola virus blood RT-PCR and lack of gastrointestinal symptoms were considered the minimum required criteria. The persistence of Ebola virus in semen 9 months after the onset of disease[7,8] necessitates condom use or avoidance of sexual intercourse, although the duration of these preventive measures have not been defined. No clear data on the virological criteria on the readmission of the convalescent person to the household, nor on commencement of social and professional activities are available.

The definition of cure of the EVD patient is an ongoing debate: a viable Ebola virus was isolated in the aqueous humour of the eye of a US patient (patient 3, table) with acute panuveitis nine weeks after Ebola virus clearance from blood.[9] In the longer term, further research is needed to assess the presence of infective viruses in EVD convalescent patients to establish evidence-based criteria and guidelines for discharge.[10] An important need exists for the scientific community to reach a consensus and develop universal guidelines using the available evidence base to define the discharge criteria for EVD patients, taking into consideration the epidemic context and available resources in low-income and high-income countries. With this aim, the INMI Lazzaro Spallanzani is starting an international consultation on the critical issues of patients' discharge outside outbreak settings.

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